Original Article

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FORMULATION AND EVALUATION OF DILTIAZEM HCL ORAL DISPERSIBLE TABLETS

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Abstract

New era of Novel Drug Delivery System oriented towards increasing safety and efficacy of existing drug molecule through novel concepts like oral drug delivery system. Orally disintegrating systems have carved a niche amongst the oral drug delivery systems due to the highest component of compliance they enjoy in patients especially the geriatrics and pediatrics. In addition, patients suffering from dysphasia, motion sickness, repeated emesis and mental disorders prefer these medications because they cannot swallow large quantity of water. Further, drugs exhibiting satisfactory absorption from the oral mucosa or intended for immediate pharmacological action can be advantageously formulated in these dosage forms. However, the requirements of formulating these dosage forms with mechanical strength sufficient to with stand the rigors of handling and capable of disintegrating within a few seconds on contact with saliva are inextricable. Diltiazem Hcl is an anti-hypertensive drug. In the present research work an attempt has been made to formulate and evaluate mouth dissolving tablets of Diltiazem Hcl . Mouth dissolving tablets of Diltiazem Hcl were prepared by direct compresion using sodium starch glycolate, croscarmellose sodium and cros-povidone as superdisintegrants. The tablets prepared were evaluated for various parameters.

Keywords: Diltiazem Hcl, Anti-hypertensive, Superdisintegrants.

Introduction

Despite of tremendous advancements in drug delivery, the oral route remains the perfect route for the administration of therapeutic agents because of low cost of therapy, ease of administration, accurate dosage, self-medication, pain avoidance, versatility, leading to high levels of patient compliance. Tablets and capsules are the most popular dosage forms. But one important drawback of such dosage forms is 'Dysphasia' or difficulty in swallowing. This is seen to afflict nearly 35% of the general population. This disorder is also associated with a number of conditions like:

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1. Parkinsonism
2. Motion sickness
3. Unconsciousness
4. Elderly patients
5. Children
6. Mentally disabled persons
7. Unavailability of water.[1]

The oral route remains the perfect route for the administration of therapeutic agents because the low cost of therapy, manufacturing and ease of administration lead to high levels of patient compliance. Many patients have difficulty swallowing tablets and hard gelatin capsules and consequently do not take medications as prescribed. It is estimated that 50% of the population is affected by this problem, which results in a high incidence of noncompliance and

ineffective therapy. The demand for solid dosage forms that can be dissolved and suspended in water, chewed, or rapidly dissolved in the mouth is particularly strong in the pediatric and geriatric markets, with further application to other patients who prefer the convenience of a readily administered dosage form[2].

Materials and Method

Various formulations of orally disintegrating tablets were developed for Diltiazem hydrochloride by direct compression method using various super disintegrants like crospovidone, sodium starch glycolate and croscarmellose sodium; filler like Mannitol as a diluent. Microcrystalline cellulose was used as a diluent. Magnesium stearate was used as lubricant and Talc as a glidant. Aspartame was added as a sweetening agent, along with a flavouring agent orange and above mixture were compressed in to fast dissolving tablets in 9 mm die, using a rotary tablet punching machine.

Evaluation of Micromeritic Properties of power blends [3,4,5]

Angle of repose

The angle of repose of powder mix for direct compression was determined by the funnel method. The powder was taken in a funnel. The height of the funnel was adjusted to 1 cm. The powder was allowed to flow through funnel freely onto the surface until the apex of the pile touches the tip of the funnel. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

Angle of repose,

$$\theta = \text{Tan-1}h/r$$

Where,

θ = angle of repose

h = height of the cone

r = radius of the cone base

Angle of repose values

Angle of repose (in degrees)	Type of flow
< 25	Excellent
25 – 30	Good
30 – 40	Satisfactory
> 40	Very poor

Bulk density

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. Powder from each formulation, previously lightly shaken to break any agglomerates formed was introduced into a measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 seconds interval. The tapping was continued until no further change in volume was noted.

Bulk density is calculated by using formula,

$$\text{Bulk density} = \frac{\text{Weight of the powder}}{\text{Bulk volume of the powder}}$$

Tapped density is calculated by using formula,

$$\text{Tapped density} = \frac{\text{Weight of the powder}}{\text{Tapped volume of the powder}}$$

Carr's index values

Carr's index (%)	Type of flow
5 – 12	Excellent
12 – 18	Good
18 – 23	Satisfactory
23 – 35	Poor
35 – 38	Very poor
> 40	Extremely poor

Carr's Index

The Carr's index of the powder mix was determined by using formula:

$$\text{Carr's index (\%)} = [(\text{TBD} - \text{LBD}) \times 100]/\text{TBD}$$

Where,

LBD = weight of the powder/volume of the packing

TBD = weight of the powder/tapped volume of the packing

Hausner's Ratio

From the LBD & TBD data Hausner's ratio was ca lculated using following equation.

Hausners ratio = LBD/TBD

Tapped Density

It was determined by placing a graduated cylinder, containing a known mass of drug-excipients blend. The cylinder was allowed to fall under its own weight onto a hard surface from the height of 10cm at 2- second intervals. The tapping was continued until no further change in volume was noted.

TBD = Weight of the powder / volume of the tapped packing.

Evaluation

Post Evaluation of Tablets [2,6,7,8]

All the formulated Diltiazem Hcl fast dissolving tablets were subjected to the following quality control tests:

1. Weight variation
2. Friability
3. Hardness
4. Disintegration
5. Wetting Time
6. In vitro dispersion time
7. In vitro Dissolution
8. Drug content
9. Thickness test

Evaluation Parameter of FDTs

Weight variation

The weight variation test is carried out in order to ensure uniformity in the weight of tablets in a batch. The total weight of 20 tablets from each formulation was determined and the average was calculated. The individual weights of the tablets were also determined accurately and the weight variation was calculated.

Hardness

The hardness of tablet is an indication of its strength. Measuring the force required to break the tablet across tests it. The force is measured in kg and the hardness of about 3-5 kg/cm^2 is considered to be satisfactory for uncoated tablets. Hardness of 10 tablets from each formulation was determined by Monsanto hardness tester.

Friability test

Friability is the loss of weight of tablet in the container due to removal of fine particles from the surface. Friability test is carried out to access the ability of the tablet to withst and brasion in packaging, handling and transport. Roche friabilator was employed for finding the friability of the tablets. 20 tablets from each formulation were weighed and placed in Roche friabilator that rotated at 25 rpm for 4 minutes. The tablets were dedusted and weighed again. The percentage of weight loss was calculated again. The percentage of weight loss was calculated using the formula

% Friability = [(W1-W2)100]/W1

Where,

W1= Weight of tablet before test

W2 = Weight of tablet after test

Disintegration test

The USP device to rest disintegration was six glass tubes that are "3 long, open at the top, and held against 10" screen at the bottom end of the basket rack assembly. One tablet is placed in each tube and the basket rack is poisoned in 1 liter beaker of distilled water at 37± 2°C, such that the tablets remain below the surface of the liquid on their upward movement and descend not closer than 2.5cm from the bottom of the beaker.

Wetting Time

The wetting time of the tablets was measured using a simple procedure. Five circular tissue papers of 10cm diameter were placed in a petridish containing 0.2% w/v solution (3ml). a tablet was carefully placed on the surface of the tissue paper. The time required for develop blue color on the upper surface of the tablets was noted as the wetting time.

Invitro Dispersion Time

Tablet was added to 10 ml of phosphate buffer solution pH 6.8 which correlates pH of saliva at 37±0.5°C and time required for complete dispersion of tablet was noted.

Uniformity of Drug Content

Five tablets were weighed and average weight is calculated. All tablets were crushed and powder equivalent to 50 mg drug was dissolved in 50 ml of phosphste buffer From the above solution 5 ml was transferred to a 10 ml standard flask and the volume is made up with phosphate buffer. Absorbance was measured at 237 nm in a UV spectrophotometer. Amount of drug present in one tablet was calculated.

Thickness

Thickness of tablets was important for uniformity of tablet size. Thickness was measured using vernier calipers on three randomly selected samples.

In vitro drug release studies

The Diltiazem Hydrochloride fast dissolving tablets were subjected to in vitro drug release studies in pH 6.8 phosphate buffer for 30 minutes to access the ability of the formulation for providing immediate drug delivery. Drug release studies were carried out in eight stage dissolution test apparatus using 900ml ml of dissolution medium (pH 6.8 phosphate buffer) maintained at 37±10C. The tablets were kept in the cylindrical basket and rotated at 50 rpm 5ml of the sample from the dissolution medium were withdrawn at each time interval for every one minute and 5ml of fresh medium was replaced each time. The samples were filtered and from the filtrate 1ml was taken and diluted to 10ml with pH 6.8 Phosphate buffer. The absorbance of the sample were measured at 237 nm using UV spectrophotometer

Results and Discussion

In the present study Diltiazem hydrochloride odt was prepared with Three different superdisintegrants namely crospovidone, sodium starch glycolate and croscarmellose were used in the formulation of fast dissolving tablets. A total of nine formulations were prepared by direct compression technique microcrystalline cellulose was used as binder. The preformulation studies such as drug polymer compatibility, bulk density, angle of repose and Carr's index evaluated were found to be within prescribed limits and indicated satisfactory free flowing property. The power blends of CP-3 batch showed excellent flowability. The data obtained from physicochemical parameters such as hardness, friability, weight variation, drug content, wetting time, in vitro dispersion time and in vitro drug release studies by CP-3 met the requirements of fast dissolving tablet technology.

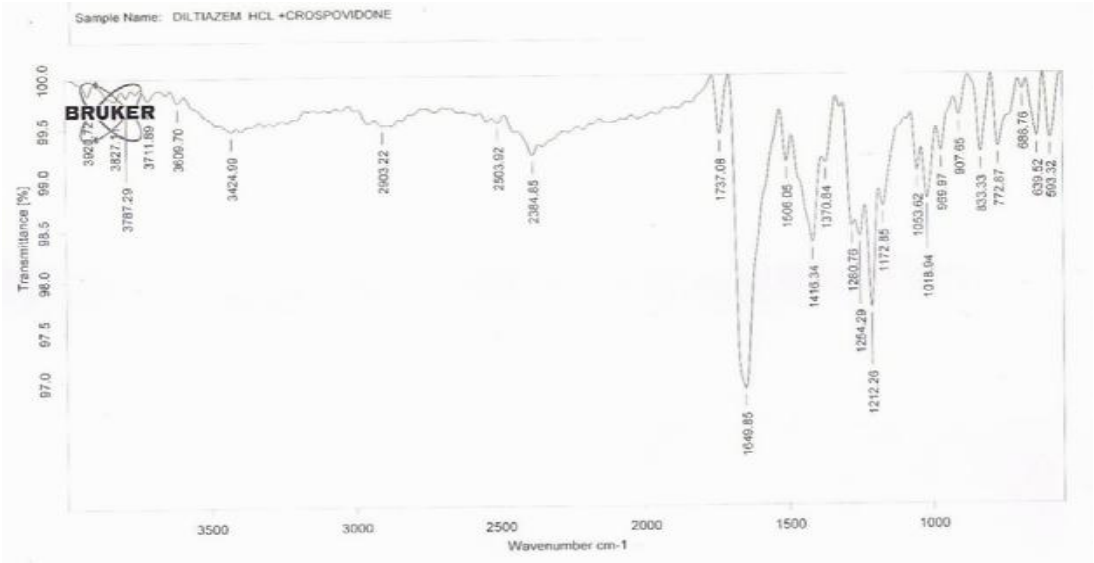

Figure 01: FT-IR Studies of Diltiazem Hcl with Crospovidone

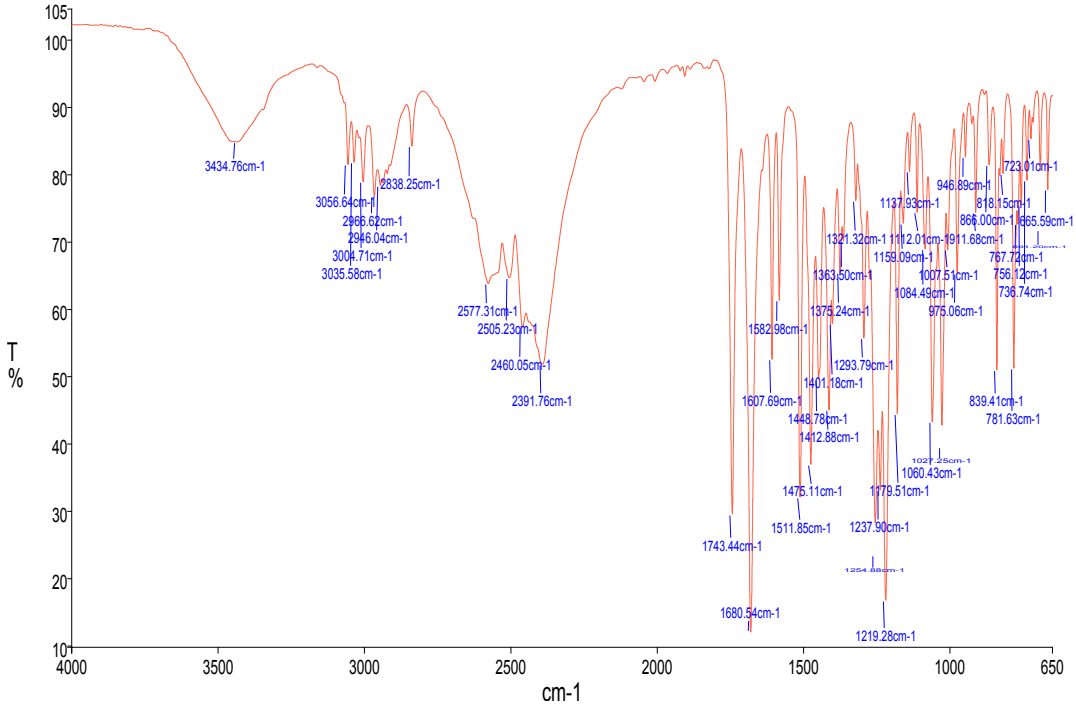

Figure 02: FT-IR of Diltiazem Hcl

Table 01: Formulation of Diltiazem Hcl Fast Dissolving Tablets

Ingredients	CP1 (mg)	CP2 (mg)	CP3 (mg)	SSG1 (mg)	SSG2 (mg)	SSG3 (mg)	CCS1 (mg)	CCS2 (mg)	CCS3 (mg)
Diltiazem Hcl	60	60	60	60	60	60	60	60	60
Crospovidone	20	24	28	-	-	-	-	-	-
Sodium starch glycolate	-	-	-	20	24	28	-	-	-
Coscarmellose sodium	-	-	-	-	-	-	20	24	28
Mannitol	179	175	171	179	175	171	179	175	171
Microcrystalline cellulose	27	27	27	27	27	27	27	27	27
Orenge flavour	2	2	2	2	2	2	2	2	2
Talc	6	6	6	6	6	6	6	6	6
Magnesium stearate	6	6	6	6	6	6	6	6	6
Total weight	300	300	300	300	300	300	300	300	300

Table 02: Composition of Disintegrating Tablets of Diltiazem Hcl

Parameters	CP-1	CP-2	CP-3	SSG-1	SSG-2	SSG-3	CCM-1	CCM-2	CCM-3
Angle of repose	28.07	23.42	21.80	29.92	27.29	24.30	27.97	25.81	21.80
Bulk density(g/ml)	0.46	0.44	0.42	0.44	0.43	0.42	0.41	0.40	0.37
Tapped density(g/ml)	0.56	0.53	0.49	0.53	0.52	0.54	0.52	0.51	0.50
Carr's index(%)	17.85	16.98	14.2	16.98	17.30	22.22	21.15	21.56	26
Haunser'ratio	1.21	1.20	1.16	1.20	1.20	1.28	1.23	1.27	1.35

Table 03: Physical Characteristics of Power Blends

Formulation No.	Wt.variation in mg	Hardness kg/cm	Thickness in mm	Wetting time in sec	Disintegration time in sec	%Friability
CP-1	299.25	3.0	3.35	79	43	0.86
CP-2	299.75	2.9	3.29	71	37	0.81
CP-3	299.65	3.2	3.18	53	28	0.41
SSG-1	300.5	3.1	3.29	94	56	0.91
SSG-2	299.5	3.0	3.38	89	48	0.66
SSG-3	299.6	3.1	3.28	65	36	0.45
CCM-1	299.75	2.9	3.41	88	47	0.55
CCM-2	299.25	2.9	3.37	81	39	0.88
CCM-3	299.5	3.0	3.24	72	34	0.63

Table 04: Evaluation of Oral Dispersible Tablets

Formulation No.	Drug content	In-vitro dispersion time(sec)	%drug release in 5min
CP-1	97.02	71	95.49
CP-2	97.68	64	96.57
CP-3	99.78	47	98.45
SSG-1	95.65	85	94.63
SSG-2	98.37	92	96.01
SSG-3	96.84	65	95.84
CCM-1	96.57	84	94.43
CCM-2	98.27	77	95.37
CCM-3	98.61	67	96.12

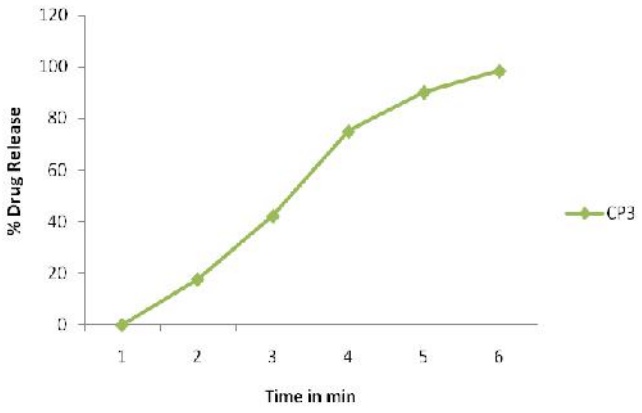

Figure 03: Drug release Profile of Diltiazem Hcl

Conclusion

In the present study, the feasibility for direct compression of powder mix of diltiazem hydrochloride and excipients was evaluated. All the batches showed good to satisfactory free flowing properties which made it suitable for direct compression. diltiazem hydrochloride obeyed Beer's law at concentrations between 2 to 10µg/ml in 6.8 pH phosphate buffer.FT-IR studies proved that superdisintegrants and all the other ingredients are compatible with diltiazem hydrochloride.All the tablets prepared showed hardness ranging from 2.9 -3.2 kg/cm2 which was sufficient to resist any mechanical pressure, it may subjected to. Among all the batches

CP-3 formulations showed the maximum hardness. CP-3 formulations showed an wetting time of 53 sec which was the minimum among all the formulations. Crospovidone was found to be the best superdisintegrant for the preparation of FDT of diltiazem hydrochloride. Thus, the objective of preparing diltiazem hydrochloride and formulating into fast dissolving tablets was successfully achieved. The formulated fast dissolving tablets of diltiazem hydrochloride may be useful for geriatric, dysphagia or non-cooperative psychiatric patients, which can improve the patient compliance and hence can minimize the premature therapeutic dropouts leading to better therapeutic efficacy.

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